

Limitation of Cardiac Output by Total Isovolumic Time During Pharmacologic Stress in Patients With Dilated Cardiomyopathy

Activation-Mediated Effects of Left Bundle Branch Block and Coronary Artery Disease

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OBJECTIVES	We sought to separate the effects of associated left bundle branch block (LBBB) and coronary artery disease (CAD) on peak cardiac output (CO) during dobutamine stress in patients with dilated cardiomyopathy (DCM).
BACKGROUND	The mechanisms limiting CO during stress in patients with DCM are unclear. Both LBBB and CAD may do so by prolonging the total isovolumic time (t-IVT).
METHODS	A total of 59 patients with DCM—34 with CAD (20 normal activation [NA], 14 LBBB) and 25 without CAD (15 NA, 10 LBBB)—were studied. The total IVT (s/min; calculated as: $60 - [\text{total ejection time} + \text{total filling time}]$) and CO were measured by Doppler echocardiography.
RESULTS	At rest, t-IVT was 8 s/min longer with LBBB ($p < 0.001$), was unaffected by CAD, and did not correlate with rest CO. During stress, CO correlated with t-IVT ($r = -0.73$, $p < 0.001$) in all four patient groups. In the absence of CAD, t-IVT became shortened (NA by 7 ± 3 s/min; LBBB by 9 ± 4 s/min) and correlated with a fall in the QRS duration (NA: $r = 0.87$; LBBB: $r = 0.91$), and CO increased with stress (NA by 4.7 ± 2.7 l/min; LBBB by 4.0 ± 2.3 l/min; all $p < 0.001$). With CAD, t-IVT did not shorten normally with stress. Instead, t-IVT was 5.6 s/min longer and CO was 3.3 l/min lower than in those without CAD (both $p < 0.001$), and t-IVT did not correlate with the QRS duration.
CONCLUSIONS	In patients with DCM, t-IVT during pharmacologic stress depends on changes in ventricular activation induced by LBBB or CAD and is, by itself, a major determinant of peak CO during stress. (J Am Coll Cardiol 2003;41:121–8) © 2003 by the American College of Cardiology Foundation

Patients with dilated cardiomyopathy (DCM) frequently have activation disturbances or underlying coronary artery disease (CAD) (1–5). When activation is abnormal, the total isovolumic time (t-IVT, or the total period, expressed in seconds per minute when the heart is neither ejecting nor filling) is characteristically prolonged at rest (6,7). Ventricular resynchronization leads to an early increase in exercise tolerance followed by a delayed rise in the ejection fraction (8–10). This clinical improvement is associated with an increase in the left ventricular (LV) total filling time, with a corresponding fall in t-IVT at rest (11).

Total IVT normally shortens during dobutamine stress (12), although in patients with CAD, this fall may be absent or even reversed (13). We therefore hypothesized that there may be an underlying relationship between t-IVT during stress and peak cardiac output (CO). In the present study, we tested this hypothesis in a group of patients with DCM studied at rest and during dobutamine stress. In particular, we wished to establish how interrelations between maxi-

mum CO and t-IVT were influenced by the presence or absence of CAD or left bundle branch block (LBBB), as well as the extent to which ventricular activation was involved.

METHODS

To identify the effect of t-IVT on CO during dobutamine stress, we designed the present study to have 80% power to detect a correlation coefficient of the order of 0.4 between t-IVT and CO at a 5% significance level. This suggested a sample size of at least 47 patients. We studied 59 patients (age 63 ± 10 years). All were selected to have DCM with a LV end-diastolic dimension >5.6 cm and end-systolic dimension >4.0 cm on the M-mode echocardiogram. Thirty-four patients had CAD (ischemic DCM, as demonstrated by at least two-vessel disease [$>70\%$ stenosis] at coronary angiography), 20 of whom had normal activation (NA: rest QRS duration <120 ms) and 14 of whom had LBBB. Left bundle branch block was diagnosed on the basis of a QRS duration >120 ms, absent Q waves, wide-slurred R waves in leads V_5 and V_6 , and monophasic QS or rS waves in leads V_1 and V_2 (14). The coronary angiograms were normal in the remaining 25 patients (idiopathic DCM), 15 of whom had NA and 10 of whom had LBBB.

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Abbreviations and Acronyms

CAD	= coronary artery disease
CO	= cardiac output
DCM	= dilated cardiomyopathy
ECG	= electrocardiogram or electrocardiographic
LBBB	= left bundle branch block
LV	= left ventricular
MR	= mitral regurgitation
NA	= normal activation
SV	= stroke volume
t-IVT	= total isovolumic time

The effects of CAD and activation were compared with those of 20 control subjects of a similar age, none of whom had a history of angina, hypertension, or diabetes. The Royal Brompton and Harefield Ethics Committee approved the study protocol. All subjects gave written, informed consent, and there were no complications related to the investigation.

Dobutamine stress protocol. Dobutamine was administered through an infusion pump (IVAC 770 syringe driver, Alaris Medical Systems, Hampshire, U.K.), starting at a rate of 5 $\mu\text{g}/\text{kg}$ body weight per min, with similar increments every 3 min to a maximum of 40 $\mu\text{g}/\text{kg}$ per min. Atropine (300 μg) was added to augment the heart rate in patients not reaching the predetermined stress end points by the end of stage 8. Systolic and diastolic blood pressures were recorded at each stage by using a Critikon Dinamap monitor (Critikon Inc., Tampa, Florida). Predetermined stress end points were: 1) 85% predicted target heart rate ($220 - \text{age in years}$) or achievement of the maximal dobutamine dose in control subjects; and 2) development of symptoms, ventricular ectopic beats, 20 mm Hg drop in systolic arterial pressure, ST-segment shift >2 mm, or T-wave inversion.

Stress echocardiography. Transthoracic echocardiography was performed using a Philips (HP) Sonos echocardiograph and a multifrequency transducer. Cross-sectional, two-dimensionally guided M-mode recordings of the LV minor axis at rest were performed using the left parasternal long-axis view, with the cursor at the tips of the mitral valve leaflets. Left ventricular minor axis dimensions were taken at end diastole (onset of the QRS complex) and at end systole at the first high-frequency vibration of the aortic component of the second heart sound on the phonocardiogram (A_2). A_2 was identified as the sound synchronous with the onset of the closure artifact on the aortic Doppler image. The LV outflow tract diameter was measured from the parasternal long-axis view and subaortic area calculated during systole (15). The transaortic Doppler echocardiogram was obtained from the apical five-chamber view. The LV ejection time was measured as the interval between the onset of forward aortic flow and the onset of the aortic closure artifact. Aortic velocity traces were digitized off line (100 Hz), and the peak aortic acceleration rate, expressed in

G ($1\text{G} = 9.81 \text{ m/s}^2$), was derived from the first differential of the velocity trace with respect to time (13). Transmitral flow velocities were recorded from the apical four-chamber view, and the filling time was measured from the onset of the E wave to the end of the A wave. Total ejection and filling periods were derived as the product of the corresponding time interval and heart rate, and these periods were expressed as seconds per minute. The t-IVT (also in s/min) was calculated as: $60 - (\text{total ejection time} + \text{total filling time})$. These values are independent of the heart rate (13). The Tei index (16) was obtained as previously described. Mitral regurgitation (MR) was graded using standard criteria: mild, moderate, or severe, according to the distance from the valve orifice that the regurgitant jet remained detectable on the color flow Doppler recording (17). Stroke distance was calculated as the time integral of aortic velocity; stroke volume (SV) as the product of stroke distance and subaortic area; and CO as the product of SV and heart rate. The wall motion score index was analyzed according to the American Society of Echocardiography's criteria (18), by an independent investigator who was unaware of the clinical history and angiographic data.

Transaortic and transmitral Doppler recordings, LV outflow tract diameter, and wall motion scores were repeated at peak stress. All tracings were acquired at a paper speed of 100 mm/s, with an electrocardiogram (ECG lead II) and phonocardiogram superimposed. An independent investigator who was unaware of the clinical history, stress ECG results, and angiographic data acquired all echocardiographic images.

Stress ECG. A standard 12-lead ECG was recorded at rest and at each stage of stress by using a Hewlett-Packard Pagewriter Xli. The frequency response of the machine was 0.05 to 150 Hz, with the baseline filter (0.4 Hz) inactivated. The ECG intervals were determined directly using built-in software and registered on a printed chart at a speed of 25 mm/s. The ST-segment shift was measured manually 80 ms after the J point.

Data analysis. Data are expressed as the mean value \pm SD. Rest and stress values within each study group were compared using a paired Student *t* test. An unpaired Student *t* test was used to compare values between control and patient groups and also to compare values between patient groups. The *p* values (statistical significance) of changes that occurred with stress within patient groups are presented in Tables 1 to 3, whereas those of differences between groups are given in the text. In view of multiple *t* tests, a significant difference was taken as $p < 0.01$. Two-way analysis of variance (ANOVA), which considered all the patients as a single group, was used to identify the individual contributions of CAD and LBBB to rest and stress values, as well as potential interactions between them. A correlation was performed by linear regression analysis, and the standard deviations of the intercepts and slopes were determined.

Table 1. Clinical Details

	Control Subjects (n = 20)	Patients With Idiopathic DCM		Patients With Ischemic DCM	
		NA (n = 15)	LBBB (n = 10)	NA (n = 20)	LBBB (n = 14)
Age (years)	65 ± 9	60 ± 13	65 ± 11	64 ± 10	63 ± 8
Male/female	8/12	12/3	8/2	18/2	13/1
EDD (cm)	5.0 ± 0.5	7.1 ± 0.8	7.0 ± 0.8	7.3 ± 0.8	7.6 ± 0.8
ESD (cm)	3.4 ± 0.5	6.1 ± 0.7	6.2 ± 0.9	6.0 ± 0.8	6.4 ± 0.9
Three-vessel CAD	0	0	0	17	12
Two-vessel CAD	0	0	0	3	2
Diuretics	0	14	8	17	11
Beta-blocker	0	4	3	7	4
ACE inhibitor	0	15	9	18	13
Stress end point					
Dobutamine dose (μg/kg per min)	39 ± 2	37 ± 4	31 ± 8*	28 ± 6†	26 ± 7
Achieved stage 8 or target HR	20	15	8	2	2
Breathlessness	0	0	2	2	1
Chest pain	0	0	0	16	2
Ventricular ectopic beats	0	0	4	2	4
Hypotensive	0	0	0	1	5
ST-segment depression	0	0	0	9	5
T-wave inversion	0	0	0	11	0

*p < 0.001 vs. control subjects (unpaired *t* test). †p < 0.01 for ischemic DCM-NA vs. idiopathic DCM/NA (unpaired *t* test). Data are presented as the mean ± SD or number of patients or control subjects. This table includes multiple end points.

ACE = angiotensin-converting enzyme; CAD = coronary artery disease; DCM = dilated cardiomyopathy; EDD = end-diastolic dimension; ESD = end-systolic dimension; HR = heart rate; LBBB = left bundle branch block; NA = normal activation.

The 95% confidence limits of correlation coefficients were determined by Z transformation.

Reproducibility. Two investigators analyzed the echocardiographic measurements, both of whom were unaware of the patients' original diagnosis and the other's findings. Intraobserver and interobserver variabilities were assessed in 20 patients (with a third individual again blinded to the original diagnosis). Duplicate measurements of ejection and filling times were made. The intraobserver coefficient of variability ranged from 3.5% to 5.2%, and the interobserver variability ranged from 4.2% to 6.4%. The reproducibility of ECG data has been previously reported (13).

RESULTS

The demographic data of the study group are presented in Table 1. There was no difference in the severity of LV

dysfunction within the DCM subgroups in terms of end-diastolic and end-systolic dimensions, in the extent and severity of CAD between ischemic DCM/NA and ischemic DCM/LBBB, or in the mean global wall motion score index at rest (idiopathic DCM: 2.35 ± 0.42 vs. 2.28 ± 0.25 , *p* = NS). The wall motion score index fell at peak stress in patients with idiopathic DCM (to 2.04 ± 0.30 , *p* < 0.001 vs. rest), but did not change in those with ischemic DCM (2.21 ± 0.54 , *p* = NS vs. rest). The stress end points also differed between groups. All control subjects and the majority of patients with idiopathic DCM/NA reached stage 8 of the stress protocol, with no symptoms or ECG changes. In all other patient groups, the test was terminated before stage 8, owing to the development of symptoms and/or ECG changes. Changes that occurred with stress within groups are presented in Table 2. The overall effects of

Table 2. Response to Dobutamine Stress: Intragroup Analysis

Variable	Control Subjects (n = 20)		Dilated Cardiomyopathy							
			NA, but No CAD (n = 15)		NA and CAD (n = 20)		LBBB, but No CAD (n = 10)		LBBB and CAD (n = 14)	
	Rest	Stress	Rest	Stress	Rest	Stress	Rest	Stress	Rest	Stress
HR (beats/min)	76 ± 12	119 ± 12*	73 ± 11	118 ± 25*	81 ± 16	112 ± 17*	72 ± 12	113 ± 19*	86 ± 19	126 ± 12*
LVET (s/min)	20 ± 3	22 ± 2†	19 ± 2	22 ± 4†	20 ± 2	22 ± 2†	18 ± 3	22 ± 2*	18 ± 3	20 ± 2
LVFT (s/min)	28 ± 4	32 ± 3*	29 ± 4	31 ± 5†	29 ± 3	29 ± 3	22 ± 4	27 ± 4†	22 ± 4	21 ± 4
t-IVT (s/min)	12 ± 2	6 ± 2*	13 ± 3	6 ± 5*	11 ± 3	9 ± 3	20 ± 3	11 ± 4*	20 ± 4	19 ± 5
Tei index	0.6 ± 0.2	0.3 ± 0.1*	0.7 ± 0.2	0.5 ± 0.2*	0.5 ± 0.2	0.4 ± 0.2	1.1 ± 0.3	0.5 ± 0.2*	1.1 ± 0.3	0.9 ± 0.3
QRS duration (ms)	93 ± 7	86 ± 7*	99 ± 8	95 ± 14*	96 ± 12	102 ± 12†	164 ± 14	156 ± 14‡	150 ± 14	152 ± 22
SV (ml)	67 ± 18	91 ± 17*	69 ± 13	85 ± 12‡	69 ± 15	66 ± 19	66 ± 12	77 ± 15‡	39 ± 15	40 ± 19
CO (l/min)	5.2 ± 1.8	10.8 ± 2.2*	4.6 ± 1.8	9.3 ± 3.2*	5.4 ± 2.3	6.7 ± 2.3†	4.8 ± 1.4	8.8 ± 1.9*	3.3 ± 1.3	4.9 ± 2.4
PAA (G)	1.3 ± 0.3	3.5 ± 0.4*	1.2 ± 0.3	2.4 ± 0.7*	1.1 ± 0.3	1.9 ± 0.6*	1.1 ± 0.3	1.7 ± 0.4*	1.0 ± 0.2	1.3 ± 0.3†

*p < 0.001, †p < 0.005, ‡p < 0.01, for stress vs. rest within group (paired *t* test). Data are presented as the mean value ± SD.

CO = cardiac output; LVET = left ventricular ejection time; LVFT = left ventricular filling time; PAA = peak aortic acceleration; SV = stroke volume; t-IVT = total isovolumic time; other abbreviations as in Table 1.

Table 3. Individual Contribution of Coronary Artery Disease and Left Bundle Branch Block by Analysis of Variance

Variable	Effect of CAD			Effect of LBBB			Interaction Between CAD and LBBB		
	F Value	Mean Diff.	p Value	F Value	Mean Diff.	p Value	F Value	Mean Diff.	p Value
Rest									
t-IVT (s/min)	—	—	—	124.1	8.0	<0.001	—	—	—
CO (l/min)	—	—	—	—	—	—	8.1	-1.6	<0.01
Stress									
t-IVT (s/min)	42.9	5.6	<0.001	53.9	7.3	<0.001	8.6	0.74	<0.01
CO (l/min)	39.5	-3.3	<0.001	7.8	-1.7	<0.01	—	—	—

F = variance ratio; — = not significant; other abbreviations as in Tables 1 and 2.

LBBB and CAD in the patient population as a whole are presented in Table 3.

Total isovolumic time. REST. The t-IVT was 12 ± 2 s/min in normal subjects and was not significantly different from normal in patients with ischemic or idiopathic DCM, provided activation was normal. In patients with LBBB, however, the t-IVT was significantly prolonged at rest (by 8 ± 3 s/min, $p < 0.001$), whether or not CAD was present (Table 3).

STRESS: EFFECT OF LBBB. In normal subjects, t-IVT became shortened by 6 ± 2 s/min with stress ($p < 0.001$) (Fig. 1). The extent of this shortening was similar in patients with normal coronary arteries (7 ± 3 s/min in idiopathic DCM/NA and 9 ± 4 s/min in idiopathic DCM/LBBB, both $p < 0.001$) (Fig. 2), but t-IVT was still 7 s/min longer in patients with LBBB than in those with NA ($p < 0.001$) (Table 3), as it started from a longer t-IVT at rest. The QRS duration fell significantly with stress when CAD was absent (7 ± 4 ms in normal subjects vs. 4 ± 2 ms in those with idiopathic DCM/NA, both $p < 0.001$; idiopathic DCM/LBBB: 8 ± 6 ms, $p < 0.01$), and in all three groups, the extent of the fall correlated with shortening of t-IVT (all $p < 0.001$) (Fig. 3).

STRESS: EFFECT OF CAD. In patients with CAD, t-IVT failed to shorten significantly with stress, regardless of whether or not LBBB was present (Fig. 2), so that overall, t-IVT was 5.6 s/min longer at peak stress when CAD was present ($p < 0.001$) (Table 3). Furthermore, in patients with CAD, the QRS duration did not fall with stress, nor did changes in individual patients correlate with those in t-IVT.

Cardiac output. REST. Only in patients with both CAD and LBBB was rest CO significantly reduced compared to normal (by 1.6 l/min; $p < 0.01$) (Table 3), as the result of an interaction between the two.

STRESS: EFFECT OF LBBB. Cardiac output increased with stress in all groups, except in patients with CAD and LBBB. In the absence of CAD, the increase in CO in patients with LBBB (4.0 ± 2.3 l/min) was not different from that in patients with NA (4.7 ± 2.7 l/min, $p = \text{NS}$). The increase in SV was similarly unaffected by activation (Table 2). The reduction in peak CO attributable to LBBB was 1.7 l/min ($p < 0.01$ by ANOVA) (Table 3).

EFFECT OF CAD. Stroke volume failed to increase with stress in patients with CAD. Furthermore, the increment in CO was lower in patients with CAD than in those with idiopathic DCM, both when activation was normal (by 3.2 ± 1.9 l/min) and with LBBB (by 2.8 ± 1.8 l/min, both $p < 0.001$). The presence of CAD reduced peak CO in the entire population by 3.3 l/min ($p < 0.001$) (Table 3).

The inotropic state. REST. Peak aortic acceleration was 1.3 ± 0.3 G in control subjects and did not differ significantly from normal in any patient group (Table 3).

STRESS. Peak aortic acceleration increased significantly with stress in each patient group ($p < 0.001$), but the extent of this increase was less in patients with idiopathic DCM/NA than in control subjects ($p < 0.01$). The increment in peak aortic acceleration was particularly low in the ischemic DCM/LBBB group, compared with the idiopathic DCM/NA group ($p < 0.01$), but did not differ from that in patients with CAD or LBBB alone.

Effect of the inotropic state and t-IVT on CO. There was no correlation between peak aortic acceleration and CO at rest ($r = 0.25$, $p = \text{NS}$) or during stress ($r = 0.32$, $p = \text{NS}$). Rest t-IVT did not correlate with either rest or peak CO during stress. However, stress CO correlated inversely with stress t-IVT. This correlation existed when all the patients were considered together ($r = -0.73$) (Fig. 4) and in all four subgroups (CAD alone: $r = -0.74$; LBBB alone: $r = -0.83$; CAD and LBBB: $r = -0.72$; all $p < 0.001$). There was no difference between them in the slope or intercept. In addition, the total filling time correlated with peak CO ($r = 0.53$, $p < 0.001$), but there was no correlation between the total ejection time and peak CO. Although the correlation of CO with t-IVT ($r = -0.73$) was higher than that with the total filling time ($r = 0.53$), the probability that they were different was $p = 0.07$. The Tei index showed a correlation with peak CO ($r = -0.68$, $p < 0.001$) similar to t-IVT alone.

Functional MR. Functional MR was detected at rest in all patients. Moderate MR became mild with stress in 12 patients and disappeared altogether in 10 more. Mild MR regressed completely in 28 patients and did not change in 4. The severity of MR did not worsen in any patient during stress.

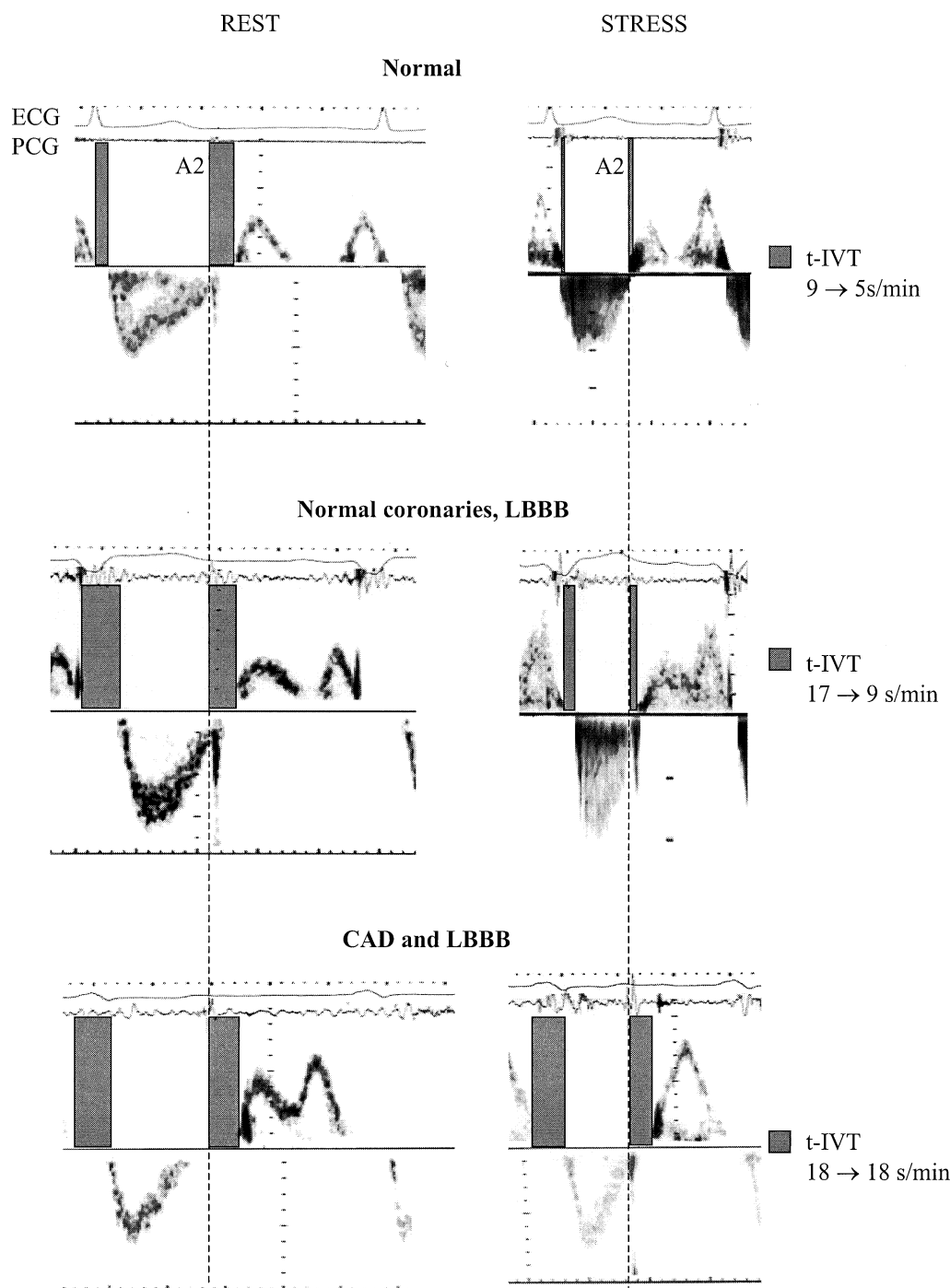


Figure 1. Superimposed aortic and mitral Doppler recordings. **(Top)** Total isovolumic time (t-IVT) normally falls with stress. **(Middle)** In left bundle branch block (LBBB), the total filling time is short and t-IVT is prolonged at rest. In the absence of coronary artery disease (CAD), t-IVT falls with stress, but does not change in patients with CAD **(bottom)**, so that one-third of the cardiac cycle is neither ejecting nor filling. A₂ = the aortic component of the second heart sound; ECG = electrocardiogram; PCG = phonocardiogram.

DISCUSSION

Total IVT and CO at peak stress. This study has demonstrated that in patients with DCM, peak CO during dobutamine stress shows a significant inverse correlation with t-IVT (Fig. 4). In many patients, t-IVT at peak stress was prolonged beyond the upper normal limit of

10 s/min, and in some it occupied a third or more of the cardiac cycle.

Prolongation of t-IVT implies a fall in either the total ejection time or total filling time, or both, during stress. We found no significant correlation between the total ejection time and peak CO, and although the total filling time showed some correlation ($r = 0.53$), that with t-IVT was

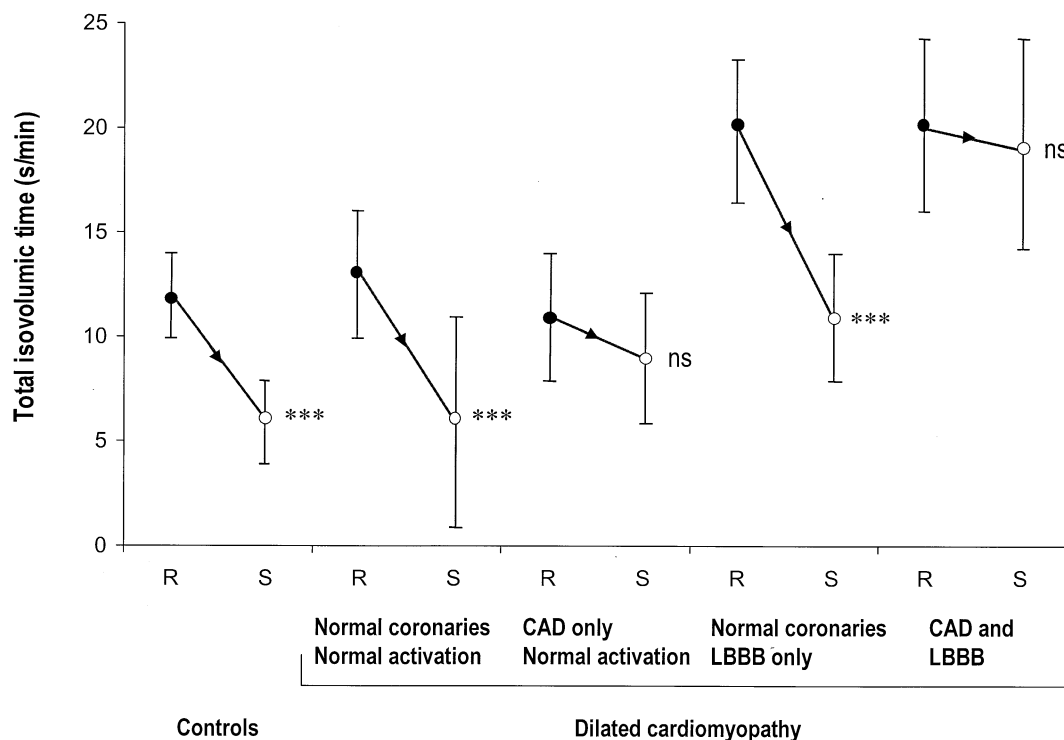


Figure 2. Total isovolumic time (IVT) at rest and peak stress in the control group and four patient groups. Total IVT was increased at peak stress in patients with left bundle branch block (LBBB) due to prolongation at rest and only shortened with stress in the absence of coronary artery disease (CAD). Data are given as the mean value \pm SD. R = rest; S = stress; ns = not significant. *** $p < 0.001$.

closer ($r = -0.73$). Thus, t-IVT appears to be the “final common pathway” in determining peak CO during stress in patients with DCM. The Tei index, which includes the ejection time (16), provided no additional information over t-IVT alone. Peak aortic acceleration, a sensitive measure of

positive inotropy, did not correlate with peak CO, despite wide variations between the groups.

Mechanisms of prolongation of t-IVT at peak stress. Both LBBB and CAD affected t-IVT at peak stress, but by different mechanisms. Total IVT was longer than normal at

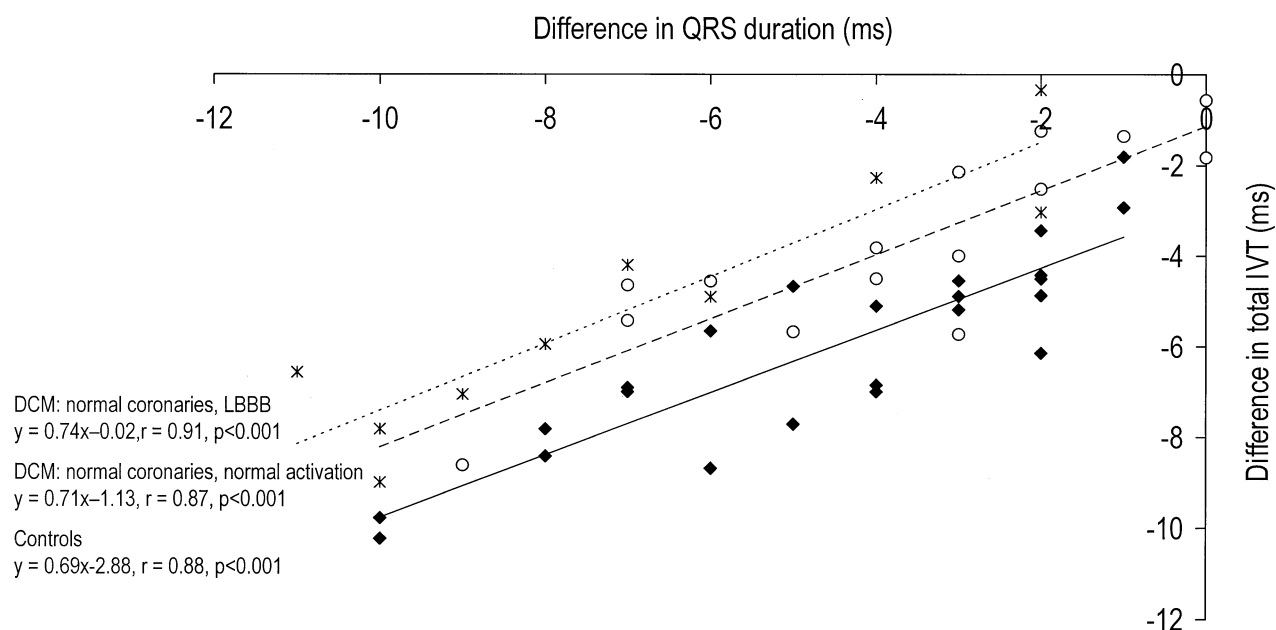


Figure 3. Correlation between changes in the QRS duration and total isovolumic time (IVT) in control subjects and patients with normal coronary arteries. In all three groups, QRS shortening was associated with a fall in t-IVT. DCM = dilated cardiomyopathy; LBBB = left bundle branch block.

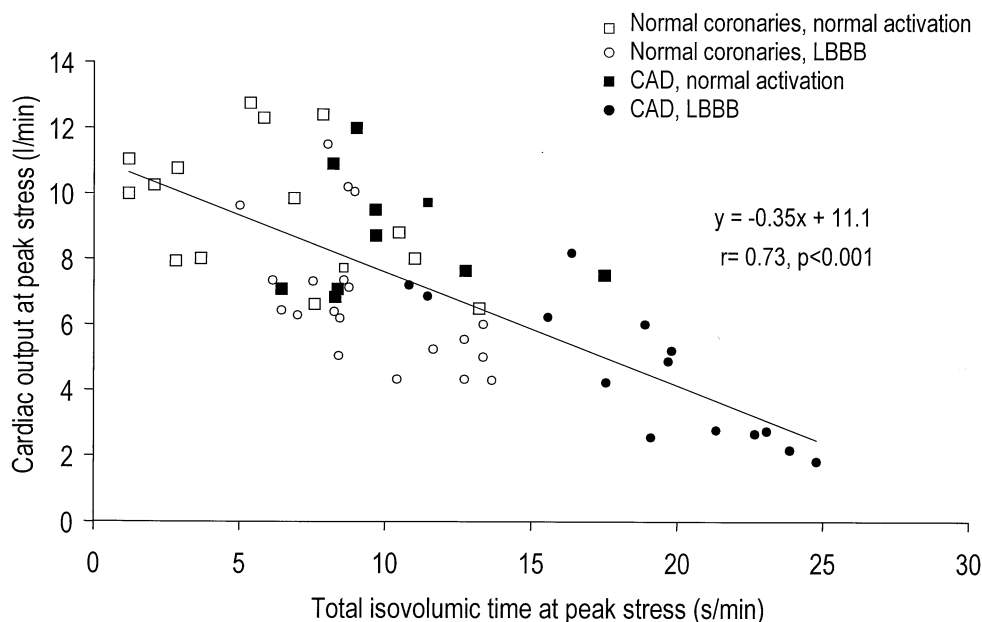


Figure 4. Correlation between peak total isovolumic time (t-IVT) and peak cardiac output (CO). Overall, peak CO correlated closely with peak t-IVT. Patients with both left bundle branch block (LBBB) and coronary artery disease (CAD) had the longest t-IVT and the lowest CO at peak stress.

rest in patients with LBBB, as previously reported (6,7), but it shortened normally with stress, provided that CAD was absent. In contrast, CAD had little, if any, effect on rest t-IVT, but it severely reduced the normal shortening with stress, whether or not LBBB was present (Fig. 2). Thus, patients with DCM with neither LBBB nor CAD had an effectively normal fall in t-IVT and an increase in CO with stress. We therefore conclude that much of the variation in peak stress-induced CO in a mixed group of patients with DCM can be related to the presence or absence of CAD and LBBB, through their effect on t-IVT.

Ventricular activation and heart failure. Total IVT, as well as its change with stress, was closely related to ventricular activation. The QRS duration normally fell with stress as t-IVT shortened, with a clear correlation between the two (Fig. 3). The same applied to patients with DCM whether or not LBBB was present, provided that the coronary arteries were normal. Indeed, this effect could be quantified, in that shortening of the QRS duration by 5 ms corresponded to a fall in t-IVT of 3.5 s/min, which, in turn, predicted an increase in peak CO of ~1.3 l/min. In patients with CAD, the QRS duration did not fall with stress, and this effect on t-IVT was additive to that of LBBB, so that when both were present, t-IVT was prolonged at rest and failed to shorten with stress. Therefore, in these patients, the longest stress values for t-IVT were observed, with peak CO approximately half that in patients with neither CAD nor LBBB. Abnormal activation, whether present at rest or occurring during stress, may thus be central to explaining the behavior of CO through its effects on t-IVT.

Study limitations. The dobutamine dose at the end point was lower in patients with CAD, so that our main conclusions are based on qualitative rather than small quantitative

differences between the groups. Limitations in assessing SV from aortic stroke distance are well recognized (15). They were minimized in the present study by using patients as their own controls and fixing the level of interrogation of the LV outflow tract. The study was not powered to differentiate rigorously between correlation coefficients, and therefore it cannot be firmly concluded that the correlation between peak CO and t-IVT ($r = -0.73$) was stronger than that between peak CO and total filling time ($r = 0.53$), at least not to a statistically significant degree. We investigated only classic LBBB, which represents a major disturbance of activation. The effects of less obvious abnormalities (e.g., absence of normal septal Q waves [19]) remain to be investigated. Finally, although it is tempting to equate the effects of dobutamine with exercise, we believe that this would be premature, as there are clear differences between the two. Nevertheless, using dobutamine, whose hemodynamic profile is well documented, permits a physiologic investigation of the LV response to an increasing heart rate and a positive inotropic stimulus, under controlled conditions.

Conclusions. Unlike the inotropic state, t-IVT proved a major determinant of CO at peak stress. The deleterious effects of LBBB and CAD on peak CO appear to be mediated through prolongation of t-IVT, albeit by different mechanisms: LBBB prolonged t-IVT at rest, whereas CAD prevented its normal shortening with stress. These separate effects could ultimately be ascribed to abnormalities in ventricular activation, so much so that peak CO was effectively normal despite marked systolic dysfunction in patients with NA at rest who showed a normal fall in the QRS duration with stress. These interrelations may have assumed therapeutic significance with the advent of resyn-

chronization therapy for heart failure, which causes a substantial fall in t-IVT in association with an increase in exercise tolerance. Similar refinements in t-IVT may be possible in patients with ischemic cardiomyopathy by revascularization or even by an electrophysiologic approach. Studying time intervals within the cardiac cycle may therefore direct appropriate therapy in individual patients with LV dysfunction, whether by resynchronization or revascularization, more securely than has previously been possible.

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